

CLINICAL THYROIDOLOGY

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JUNE 2009

EDITOR'S COMMENTS 2

CONCISE REVIEW

TSH Abnormalities and Fetal Loss 3

THYROID FUNCTION IN PREGNANCY

Pregnant women with high serum TSH levels without overt thyroid dysfunction have an increased risk of miscarriage

Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009; 160:985-91. 8

HYPOTHYROIDISM

Reference limits for serum TSH differ significantly between races and with age, potentially causing erroneous diagnosis in a substantial number of patients

Boucai L, Surks MI. Reference limits of serum TSH and free T₄ are significantly influenced by race and age in an urban outpatient medical practice. *Clin Endocrinol (Oxf)* 2009;70:788-93. 10

MULTINODULAR GOITER

The optimal time interval to increase radioiodine uptake in a multinodular goiter is 24 hours after recombinant human thyrotropin administration

Fast S, Nielsen VE, Grupe P, Bonnema SJ, Hegedus L. Optimizing ¹³¹I uptake after rhTSH Stimulation in patients with nontoxic multinodular goiter: evidence from a prospective, randomized, double-blind study. *J Nucl Med* 2009;50:732-7. 13

GRAVES' DISEASE

Anemia in Graves' disease is common and resembles the anemia of chronic disease

Gianoukakis AG, Leigh MJ, Richards P, Christenson PD, Hakimian A, Fu P, Niihara Y, Smith TJ. Characterization of the anaemia associated with Graves' disease. *Clin Endocrinol (Oxf)* 2009;70:781-7. 15

THYROID CANCER

Preparation for ¹³¹I remnant ablation with 54 mCi is equally effective with thyroid hormone withdrawal and recombinant human TSH

Chianelli M, Chianelli M, Todino V, Graziano FM, Panunzi C, Pace D, Guglielmi R, Signore A, Papini E. Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. *Eur J Endocrinol* 2009;160:431-6. 18

REVIEW ARTICLES & HOT NEW ARTICLES

REVIEWS 21
HOT NEW ARTICLES 21
DISCLOSURE 21

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EDITOR'S COMMENTS

This is the sixth 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you by email as a separate list of articles that can be downloaded individually or as the entire document.

CONCISE REVIEW We wish to thank Dr. Alex Stagnaro-Green for contributing a review on TSH Abnormalities and Fetal Loss in this issue of *Clinical Thyroidology*. This is a unique review of a difficult issue written by an expert in the field that you will find helpful in day-to-day practice.

SEARCH FOR PREVIOUS ISSUES of *Clinical Thyroidology* A number of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as thyroid cancer, or other terms. You will find this by simply right clicking the following: <http://thyroid.org/professionals/publications/clinthy/index.html>

FIGURES You will notice that the articles in *Clinical Thyroidology* contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page now has a set of references to **REVIEWS & HOT ARTICLES** which contains references to important reviews and very recent articles that look especially important to the Editors.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in entirety.

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS Beginning with the first review article for *Clinical Thyroidology* by Dr. Elaine Ron, authors can cite our **CONCISE REVIEWS** by using the electronic citation at the end of each review.

Ernest L. Mazzaferri, MD, MACP

Jennifer A. Sipos, MD

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[Back to Contents](#)

TSH Abnormalities and Fetal Loss

INTRODUCTION

The present review will examine the impact of maternal serum thyrotropin (TSH) abnormalities on fetal loss (defined as spontaneous miscarriage, intrauterine death and neonatal death). This interaction, and the potential to prevent fetal loss with appropriate intervention, is one of the core issues of the ongoing debate regarding universal screening during pregnancy for thyroid disease. Although the majority of the literature has centered on hypothyroidism, and in particular subclinical hypothyroidism, an important literature also exists on the interaction of fetal demise and hyperthyroidism. In 1969, Jones and Man published a landmark article evaluating the impact of abnormal serum butanol-extractable iodine (BEI) levels and miscarriage, premature deliveries and stillbirths. Low BEIs, consistent with hypothyroidism, was reported in 6% (60/1000) of the women evaluated. Women with low BEIs had a significant increase in miscarriages, prematurity and stillbirths compared to 1,255 women with normal BEIs during pregnancy (1). Similarly, women with elevated BEIs, consistent with hyperthyroidism, had an increase in deliveries without full-term surviving infants compared to controls (31.8% vs. 12.6% respectively).

INCIDENCE

Nine studies have evaluated the incidence of hypothyroidism during pregnancy (2-10). As demonstrated in Table 1, the studies vary in their definition of hypothyroidism, along with the time of pregnancy at which screening occurred. Two studies evaluated less than 1000 women, raising questions of the validity of their findings (5, 10). Investigations performed in the United States (excluding the study with only 209 subjects) have yielded remarkably similar results. Overall, the incidence of hypothyroidism was between 2.2% to 2.5%, with an incidence of subclinical and overt hypothyroidism ranging from 2.2% to 2.3% and 0.2% to 0.3% respectively. The overall rate of hypothyroidism in the United Kingdom was similar at 2.6%, however there was an increased incidence of overt hypothyroidism at 1.0%. Studies in Finland, the Netherlands, and India have yielded disparate results with rates of hypothyroidism of 4.8%, 0.5%, and 11.1% respectively.

Determination of the incidence of hyperthyroidism in pregnancy is complicated by the normal physiological increase in human chorionic gonadotropin (hCG) which occurs in the first half of pregnancy. Due to cross reactivity of hCG at the TSH receptor, a percentage of pregnant women will develop a transiently suppressed serum TSH. In order to grapple with this issue, studies have attempted to differentiate women with low serum TSH during pregnancy secondary to hCG stimulation, from those individuals with TSH values which are suppressed secondary to ongoing thyroid disease. As demonstrated in Table 2, (5, 6, 8, 9, 10-14), low TSH values can be found in up to 34% of all pregnancies. However, suppressed serum TSH levels, those below $<0.03 \mu\text{IU/ml}$, is found in 2% of pregnant women. The majority of these women present with subclinical, as opposed to overt, hyperthyroidism.

Finally, a small, but undefined, percentage of women who become pregnant will already be on treatment for previously diagnosed hypothyroidism or hyperthyroidism. As documented in the Colorado Thyroid Disease Prevalence Study, a statewide health fair conducted in 1995 with 25,862 participants, only 60% of individuals treated with thyroid medication ($n=1525$) were euthyroid at the time of screening (15). Given the well documented need to increase the dose of levothyroxine during pregnancy in the majority of women (16, 17), it is not surprising that Hallengren et al found 49% of pregnant women on levothyroxine therapy (31/63) had TSH values outside the reference range (18). In particular, 12 women had TSH values below $0.40 \mu\text{IU/ml}$ and 19 women had TSH levels which exceeded $4.0 \mu\text{IU/ml}$. Similar results were reported in the FaSTER (First and Second Trimester Evaluation of Risk for Fetal aneuploid) trial, which evaluated first and second trimester TSH levels in 389 pregnant women with a diagnosis of hypothyroidism. Forty-three percent of women had a TSH above $2.5 \mu\text{IU/ml}$ in the first trimester and 33% of women had a TSH exceeding $3.0 \mu\text{IU/ml}$ in the second trimester (19).

FETAL LOSS-HYPOTHYROIDISM

Thirteen articles have investigated the relationship between fetal loss and hypothyroidism. The studies vary markedly in the following criteria: number of women enrolled, gestational week of enrollment; definition of thyroid dysfunction; treatment and when initiated; and retrospective vs. prospective. Studies in which information is not provided on the gestational week of initial thyroid sampling may have misleading data on the incidence of miscarriage (for example, if initial screening occurred at 16 weeks most miscarriages would have already occurred). Three retrospective clinical series are reported in the following paragraph.

In one of the earliest reports (1981), Montoro et al describe the outcome of 9 hypothyroid women during 11 pregnancies. In their study, the incidence of fetal death was 10% ($n=1$) (20). Davis et al reported on 28 pregnancies in 25 women who were hypothyroid during pregnancy. Sixteen women were clinically hypothyroid and 12 women presented with subclinical hypothyroidism (21). Levothyroxine intervention occurred in 26 of the pregnancies and was initiated at varying times (between 4-40 weeks gestation). Fetal death occurred in one individual with subclinical hypothyroidism (1/12 or 8%) and two women with clinical hypothyroidism (2/16 or 13%). A similar, but larger series was published by Leung et al, in which 68 women with overt ($n=23$) and subclinical ($n=48$) hypothyroidism were followed prospectively (22). One fetal death occurred in a woman (1/23=4%) who had discontinued levothyroxine therapy, resulting in a TSH of $289 \mu\text{IU/ml}$.

Table 3 summarizes nine articles which will be described in the remainder of this section. Allan et al evaluated TSH levels and miscarriage in 9,403 women who were screened for neural tube defects and Down's syndrome (3). They reported that second

trimester miscarriages were increased four-fold in women with elevated TSH levels as compared to controls. In hypothyroid women, the greatest increase in miscarriage was seen in individuals whose TSH was $\geq 10.0 \mu\text{IU/ml}$ as compared to women with TSH values between 6.0 mU/L and $9.99 \mu\text{IU/ml}$ (8.1% vs. 2.9% respectively). Abalovich et al followed 150 pregnancies in 114 women who were being treated for hypothyroidism (23). The outcome of the 51 pregnancies conceived while the woman was hypothyroid was compared to the 99 pregnancies conceived in euthyroid women. Women who were adequately treated during pregnancy had a marked decrease in miscarriages as compared to women who were inadequately replaced with levothyroxine.

Casey et al reported on pregnancy outcome of 17,298 women screened for thyroid disease prior to the 20th week of pregnancy (4). No difference in the rate of fetal death between women with subclinical hypothyroidism and controls was found. They also reported no increase in fetal deaths in women with isolated hypothyroxinemia (normal TSH and decreased free T_4) (24). Similar findings were described by Matalon et al. One thousand one hundred and two deliveries, out of 139,168 deliveries, were in hypothyroid women. The perinatal death rate in the two groups was virtually identical (25).

In 2008 Cleary-Goldman et al published an analysis of pregnancy outcome and thyroid function in the 10,990 women who participated in the FaSTER trial (7). Designed to study first trimester ultrasound translucency measurements, along with first and second trimester serum markers for Down syndrome, TSH and free T_4 values were analyzed in all women. As compared to controls, neither miscarriage nor fetal death was related to thyroid function levels in either trimester.

Four studies have already been published in 2009 evaluating the relationship between thyroid dysfunction and fetal demise. Sahu et al reported an increase in intrauterine demise in women with overt hypothyroidism, but not subclinical hypothyroidism, as compared to controls (10). On the other hand, Mannisto et al reported no difference in miscarriage or perinatal mortality rates between controls and women with either subclinical or clinical hypothyroidism (8). Hallengren et al reported on pregnancy outcome in 63 women on thyroid replacement therapy. Fetal loss was significantly greater in women with abnormal thyroid function (either hypothyroidism or hyperthyroidism) as compared to women who were euthyroid on replacement (29% vs. 6%, $p < 0.05$) (18). Finally, in a prospective study, Benhadi et al evaluated the impact of increased maternal serum TSH levels with subsequent child loss, defined as a combination of miscarriage, fetal and neonatal death (this study not included in Table 3). A positive linear relationship was reported between child loss and TSH, which extended into the normal TSH range (9).

FETAL LOSS-HYPERTHYROIDISM

Few studies have investigated the association between hyperthyroidism and fetal loss. As a component of their previously described cohort, Casey et al examined the relationship between subclinical hyperthyroidism and pregnancy outcomes (13). Of the 25,765 women screened, 433 presented with subclinical hyperthyroidism (1.7%). The rate of neonatal death between these two groups was indistinguishable (0.2% vs. 0.2%, $p = \text{ns}$). Similarly, Mannisto reported similar rates of miscarriage and perinatal mortality in women with hyperthyroidism (either overt or subclinical) as contrasted to controls (8). Anselmo et al evaluated the fetal impact of thyroid hormone excess by analyzing fetal outcome in mothers with thyroid hormone resistance (THR) (26). An increased miscarriage rate was seen in mothers affected by THR. This may have preferentially impacted fetuses that were unaffected by THR. Unaffected infants with THR mothers had suppressed TSH levels at birth and decreased birth weights, further demonstrating the impact of excess thyroid hormone on the developing fetus.

CONCLUSION

In conclusion, the incidence of thyroid dysfunction, defined as either hypothyroidism or hyperthyroidism during pregnancy, is approximately 5%, or one out of every 20 women. The relationship between thyroid dysfunction and fetal demise remains murky. No relationship exists in women with subclinical hyperthyroidism, and the studies in overt hyperthyroidism are mixed. The picture is even more confusing in respect to hypothyroidism. Overt hypothyroidism appears to be linked to fetal demise, but whether or not a relationship exists between fetal demise and subclinical hypothyroidism is simply unclear. Specifically, the published studies to date are evenly split between those that have, and have not, found a relationship between subclinical hypothyroidism and fetal demise. The increasing rate of fetal loss as maternal serum TSH rises through the normal range documented by Benhadi et al, challenges us to question what is considered a normal TSH. Much light will be shed on the relationship between fetal loss and thyroid dysfunction in the ensuing five years. Research is increasing at a rapid rate, and ongoing prospective studies in Cardiff, the NIH and Lecce will yield much needed clarity.

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Table 1. Nine Studies that evaluated the incidence of hypothyroidism during pregnancy

Author	Year	N	Country	Gestational Week	TSH	T ₄	Hypothyroidism Subclinical Overt	
Klein et al (2)	1991	2000	USA	15-18 weeks	>6 mU/L	<2 SD	2.2%	0.3%
Allan et al (3)	2000	9403	USA	15-18 weeks	>6 mU/L	NR	2.2%	
Casey et al (4)	2005	17,298	USA	<20 weeks	>97.5th percentile	<0.680 ng/dl	2.3%	0.2%
Aoki et al (5)	2007	209	USA		>5.0 mU/L		6.9%	
Vaidya et al (6)	2007	1560	UK	Median 9th week	>4.3 μIU/ml	<12.0 pmol/l	1.6%	1.0%
Cleary-Goldman et al (7)	2008	10,990	USA	1st Trimester	>97.5th percentile	<2.5th percentile	2.2%	0.3%
Mannisto et al (8)	2009	5,805	Finland	12th week	>95th percentile	<5th percentile	3.9%	0.9%
Benhadi et al (9)	2009	2,497	Netherlands	Mean 13th week	>5.6 mU/L	<7.5 pmol/L	0.5%	
Sahu et al (10)	2009	633	India	13-26 weeks	>5.5 mU/L	NR	6.5%	4.6%

NR = Not reported; SD = standard deviation; Gestational week = the gestational week during pregnancy that the sample was obtained.

Table 2. Nine studies that evaluated the incidence of hyperthyroidism during pregnancy

Author	Year	N	Country	Gestational Week	TSH μIU/ml	T ₄ pmol/L	Hyperthyroidism Subclinical Overt	
Glinoeer (11)	1997	760	Belgium	8-14 weeks	<0.02 μIU/ml	>26.0		2.4%
Yeo et al (12)	2001	184	Singapore	8-14 weeks	<0.36 mU/L	>19.1	22%	12%
Casey et al (13)	2006	25,765	USA	<20 weeks	<2.5th percentile	>1.75 (ng/dl)	1.7%	0.4%
Aoki et al (5)	2007	209	USA		<0.1 μIU/ml		2.9%	
Vaidya et al (6)	2007	1560	United Kingdom	Median 9th week	<0.03 μIU/ml	>23.0	1.2%	0.7%
Lazarus & Kahelamanon (14)	2007	1497	United Kingdom	9-15 weeks	<0.02 μIU/ml	>23.1	1.3%	0.17%
Mannisto et al (8)	2009	5805	Finland	12th week	<95th percentile	>5th percentile	3.5%	1.3%
Benhadi et al (9)	2009	2,497	Netherlands	Mean 13th week	<0.34 μIU/ml	>21.1	5.0%	0%
Sahu et al (10)	2009	633	India	Mean 13th week	<0.5 mU/L	NR	0.9%	0.8%

NR = not reported; TSH = μIU/ml; FT₄ = free thyroxine (pmol/L) or ng/dl in one study as noted; Gestational week = the gestational week during pregnancy that the sample was obtained

Table 3. Nine studies that evaluated the relationship between hypothyroidism and fetal demise

Author	Year	Country	Total	Number Hypothyroid	Thyroid	Miscarriage Hypothyroid	Miscarriage Control	Fetal Death Hypothyroid	Fetal Death Control	Weeks Gestation	P
Allan et al (3)	2000	USA	9,403	209	Hypothyroidism definition TSH > 6 μ IU/ml	3.8%	0.9%	NR	NR	15-18 weeks	<0.05
Abalovich et al (23)	2002	Argentina	150	35 - Subclinical 16 - Overt	Adequate Rx TSH > 97.5 th percentile T ₄ < 0.680 ng/dl	60% - Overt 71% - Subclinical	0% - Overt 0% - Subclinical	NR	NR	NR	P < 0.006
Casey et al (4)	2005	USA	17,298	404	Subclinical Hypothyroidism TSH > 97.5 th percentile T ₄ < 0.680 ng/dl	NR	NR	0.5%	0.5%	<20 weeks	NS
Matalon et al (25)	2006	Israel	139,168	1,102				1.4%	1.3%		NS
Casey et al (24)	2007	USA	17,298	233	Isolated Hypothyroxenemia TSH 2.5 th - 97.5 th T ₄ < 0.680 ng/dl	NR	NR	0%	0.5%	<20 weeks	NS
Cleary-Goldman et al (7)	2008	USA	10,990	240 - Subclinical 243 - Hypothyroid	Subclinical Hypothyroidism TSH > 97.5 th Normal fT ₄	0.4% - Subclinical 0.0% - Hypothyroid	0.6%	0.0% - Subclinical 0.4% - Hypothyroid	0.3%	1st Trimester	NS
Sahu et al (10)	2009	India	633	41 - Subclinical 29 - Clinical hypothyroidism	Subclinical Hypothyroidism TSH > 5.5 μ IU/ml Normal fT ₄	NR	NR	25% - Subclinical 13% - Overt	1.4%	13-26 weeks	NS p=0.0004
Mannisto et al (8)	2009	Finland	5,805	224 - Subclinical 54 - Clinical	Subclinical Hypothyroidism TSH > 95 th Normal fT ₄	Subcl - 16.1% Clin - 22.2%	19.5%	Subcl - 1.8% Overt - 1.9%	0.8%	12 th week	NS
Hallengren et al (18)	2009	Sweden	63	19 - Hypothyroidism 12 - Hyperthyroidism	Normal TSH 0.4 - 4.0 μ IU/ml	NR	NR	Euthyroid - 6% Hypothyroid or Hyperthyroid - 29%		1st Trimester	p < 0.05

NR = not reported
fT₄ = Free thyroxine
Wks = weeks

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Pregnant women with high serum TSH levels without overt thyroid dysfunction have an increased risk of miscarriage

Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009;160:985-91.

SUMMARY

BACKGROUND Thyroid hormones are critical for the development of the fetal brain during early postnatal life. One study has shown that thyrotropin (TSH) levels above 6 $\mu\text{IU/ml}$ are associated with a significantly higher rate of stillbirth, and from the second trimester onward, the main adverse obstetrical outcome is an increased of fetal death. In addition, women with high free thyroxine (FT_4) levels accompanied with normal or slightly elevated serum TSH levels have a higher rate of miscarriage. The purpose of this study was to examine the association between maternal serum TSH and FT_4 levels and the presence of thyroid peroxidase antibodies (TPOAb) in pregnancy, and the rate of subsequent fetal loss.

METHODS The study was performed using data from pregnant Dutch women without known thyroid disease who participated in the Amsterdam Born Children and their Development (ABCD) study in Amsterdam from March 2003 through January 2004. This is a collaborative effort of the Municipal Health Services and all hospitals and midwife practices in Amsterdam. The main aim of the ABCD study was to examine the differences in pregnancy outcomes by focusing on maternal ethnic background, lifestyle, and psychosocial conditions as they relate to pregnancy outcome and the baby's health. Of 12,377 pregnant Dutch women queried, 8266 (67%) agreed to participate in the study by filling out a questionnaire that included questions about social demographic characteristics and ethnic background. Other ethnic groups were excluded from the analysis because of

the significant differences in serum TSH and pregnancy outcome among various ethnic groups. In addition, 4267 women provided consent for blood collection during their first obstetrics visit, which on average took place during the 13th week of gestation. Miscarriage, fetal death, or neonatal death was determined from three overlapping sources: (1) the National Midwife Registry, (2) the National Obstetricians Registry, and (3) the National Neonatal Registry. Miscarriage was defined as fetal death occurring before 22 weeks of gestation. Fetal death was defined as death occurring from 22 weeks of gestation until delivery, and neonatal death from 0 to 7 days after delivery, including stillbirth and intrauterine deaths. Overt hyperthyroidism was defined as a TSH concentration less than 0.35 $\mu\text{IU/ml}$ with an FT_4 above the upper limit of normal (21.1 pmol/L). Overt hypothyroidism was defined as a TSH above 5.60 $\mu\text{IU/ml}$ with a FT_4 below the lower limit of normal (7.5 pmol/L).

RESULTS A total of 2497 women remained in the study after excluding 116 who had blood samples that were either unacceptable or had missing TSH values. The mean age ($\pm\text{SD}$) of the study group was 32 ± 4.0 years. This was the first pregnancy in 60% of the women and the second in 32%. A total of 230 women (9.2%) smoked during their pregnancy. The serum TSH was less than 3.4 $\mu\text{IU/ml}$ in 129 women (5%) and was 5.6 $\mu\text{IU/ml}$ or higher in 11 women (0.5%). Among 95 women (4%), the FT_4 concentration was less than 7.5 pmol/L, and none had an FT_4 value above 21.1 pmol/L. TPOAb was elevated (>80 kU/L) in 146 of 2497 women (5.8%). TSH and FT_4 concentrations were

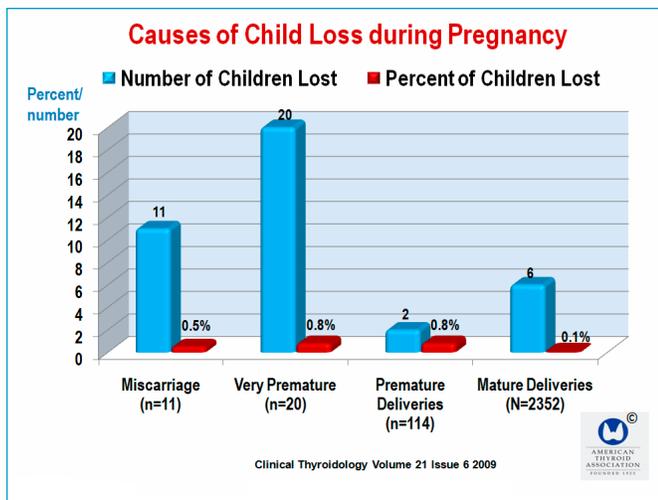


Figure 1. The rate of child loss is shown in this figure. Miscarriage was defined as death of the fetus occurring before 22 weeks of gestation. Fetal death and neonatal death were defined according to existing standards: fetal death = death occurring from 22 weeks of gestation until delivery; neonatal death = death from 0 to 7 days after delivery. Fetal death includes stillbirth and intrauterine deaths in this cohort. The numbers in parentheses in the horizontal axis are the number of events. (Derived from data in Table 2A of Benhadi et al.)

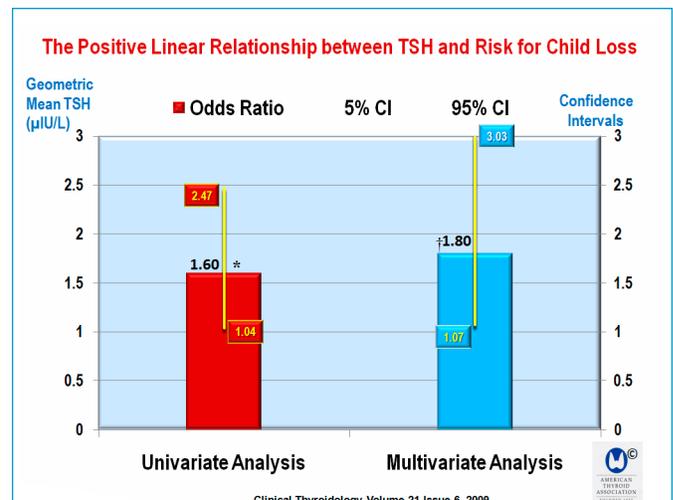
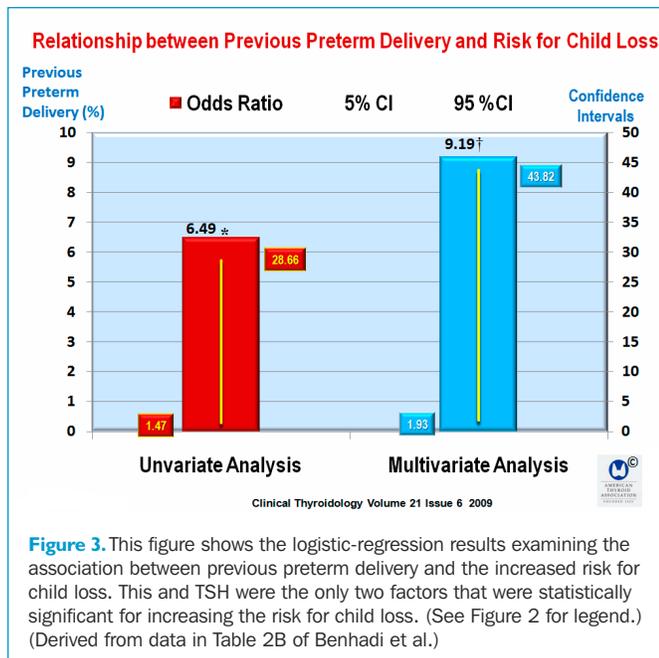


Figure 2. The log-transformed TSH level was related to child loss (OR, 1.60 for every doubling in TSH concentration; 95% CI, 1.04 to 2.47; *P = 0.033). After multivariate analysis, the effect of TSH had an OR of 1.80 (95% CI, 1.07 to 3.03; †P = 0.027 for OR). The yellow bars are 5% and 95% Confidence intervals. The small red and blue boxes contain the confidence intervals. (Derived from data in Table 2A of Benhadi et al.)

negatively correlated (Pearson's $r = -0.375$, $P < 0.001$) and the TPOAb concentration was positively correlated with TSH ($r = 0.32$, $P < 0.001$) and negatively with FT_4 ($r = -0.065$, $P < 0.001$).

The median TSH concentration in women without serum TPOAb was $1.17 \mu\text{IU/ml}$ (interquartile range [IQR], 0.80 to 1.70), and it was $2.16 \mu\text{IU/ml}$ (IQR, 1.27 to 3.38) in women with serum TPOAb. The median FT_4 concentrations were 9.59 pmol/L (IQR, 8.81 to 10.43) and 9.00 pmol/L (IQR, 8.16 to 10.17), respectively. The difference between the TPOAb-positive and TPOAb-negative women was significant for both TSH and FT_4 ($P < 0.001$).



A total of 11 women had a miscarriage (0.5%). There were 20 very premature deliveries (<32 weeks) (0.8%), 114 premature deliveries (32 to 36 weeks) (4.6%), and 2325 mature deliveries (>36 weeks) (93%). The infant died in 8 (0.3%), 2 (0.8%), and 6 (0.1%) cases, respectively (Figure 1). In all, there were 27 miscarriages, fetal deaths, or neonatal deaths. Five women were excluded from the analysis because their pregnancies were terminated for various reasons.

There was a positive linear relationship between the log-transformed TSH values and the risk for subsequent child loss. In univariate analysis, the TSH concentration was related to child loss (odds ratio [OR], 1.60 for every doubling in TSH concentration; 95% confidence interval [CI], 1.04 to 2.47; $P = 0.033$) (Figure 2). The effect of TSH had an OR of 1.80 (95% CI, 1.07 to 3.03; $P = 0.027$) after adjustment for smoking, parity, age, diabetes mellitus, hypertension, previous stillbirth/miscarriage, or previous preterm delivery and TPOAb positivity. The authors emphasized that while the increased relative risk was substantial, the absolute risks were small. For example, for a mother with a serum TSH level of $0.54 \mu\text{IU/ml}$ (10th percentile of the study population) the estimated absolute risk would be 0.8%, while the expected risk for a woman with a TSH of $3.12 \mu\text{IU/ml}$ (90th percentile) would be 2.2%. The relationship between serum FT_4 concentrations and child loss was not statistically significant. Of the other factors included in the analysis, a previous preterm delivery was the only factor other than TSH that was significantly associated with child loss (Figure 3).

CONCLUSIONS Pregnant women with high TSH levels without overt thyroid dysfunction and previous preterm delivery are independent factors that increase the risk of miscarriage; however, maternal FT_4 concentrations are not associated with fetal loss.

COMMENTARY

Severe maternal thyroxine deficiency is well known to be associated with poor obstetric outcomes. In 1991, Klein et al. (1) reported that 49 of 2000 consecutive woman (2.5%) living in Maine who were being tested for α -fetoprotein concentration had serum TSH concentrations above $6 \mu\text{IU/ml}$ during gestational weeks 15 to 18. Six of these women had elevated TSH concentrations, ranging from 6.9 to $54 \mu\text{IU/ml}$, with serum T_4 concentrations that were more than 2 SD below average, underscoring the high prevalence of hypothyroidism in pregnant women. In 2000, Allan et al. (2) found that among 9403 women with singleton pregnancies, TSH measurements were $6 \mu\text{IU/ml}$ or higher in 209 women (2.2%). The fetal death rate in these women was significantly higher (3.8%) than that in women with TSH levels less than $6 \mu\text{IU/ml}$ (0.9%; OR, 4.4; 95% CI, 1.9 to 9.5). Still, other pregnancy complications did not occur

more frequently. Klein et al. concluded that the major adverse obstetrical outcome of an elevated serum TSH concentration from the second trimester onward is an increased rate of fetal death. Benhadi et al. found that the risk for child loss not only increased with higher TSH levels, but occurred even when maternal FT_4 concentrations were normal. The large sample size in this study demonstrates the risk for child loss with higher TSH concentrations alone, and raises the idea that pregnancy outcome might be improved by levothyroxine treatment.

The Concise Review in this issue of Clinical Thyroidology by Dr. Alex Stagnaro-Green puts the study by Benhadi et al. in perspective, including the idea of levothyroxine therapy.

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Reference limits for serum TSH differ significantly between races and with age, potentially causing erroneous diagnosis in a substantial number of patients

Boucai L, Surks MI. Reference limits of serum TSH and free T₄ are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf) 2009;70:788-93.

SUMMARY

BACKGROUND The upper reference limit of serum thyrotropin (TSH) is the subject of considerable controversy. As a result, the TSH reference limits derived from national databases have not yet been uniformly applied to clinical practice. This study is aimed at determining whether race and age influence the distribution of TSH and free thyroxine (FT₄). Although serum TSH reference limits have traditionally been established in individuals free of thyroid disease without antithyroid antibodies, more recent studies of thyroid disease-free subjects have found no difference in the median TSH and the 97.5th centile when individuals with antithyroid antibodies and even ultrasound abnormalities were excluded. Furthermore, analysis of the National Health and Nutrition Examination Survey III (NHANES III) found that age-related shifts in TSH distribution were not significantly altered by excluding individuals with antithyroid antibodies. These new findings thus suggest that TSH reference limits can now be assessed in populations deemed not to have thyroid disease on clinical grounds, without knowing the individual's antithyroid antibody status.

METHODS This is a cross-sectional study of the outpatient medical practices of the Montefiore Medical Center, Bronx, New York. Among 119,361 outpatients seen from January 1 through December 31, 2006, a total of 46,183 (38%) had TSH determinations. A total of 22,116 patients comprised the study group after excluding patients with International Classification of Diseases, 9th edition (ICD-9) codes for all thyroid diseases and those taking medications that affect FT₄ and TSH. Of the study group, 16,343 were female (74%) and 5773 were male (26%), and all were older than 10 years of age. The adult population was represented by 18,243 patients (83%) older than 20 years of age, only 3.8% of whom had tests for antithyroid antibodies. The median age of the adult group was 44 years, and of this group, 17,787 (98%) had simultaneous TSH and FT₄ determinations. Self-designated race/ethnicity, which was available in 11,604 patients (52.5%), was designated as black or African American in 32.8%, white in 14.7%, Hispanic in 5%, and undesignated in 47.5%. The Bronx has different demographics than occur nationally, reflected by the median age (31.2 years vs. 36.2 years), the percentage <44 years of age (71 vs. 65.5), and the percentage of whites (29.2 vs. 75%), blacks (35.6 vs 12.3), and Hispanics (48.4 vs. 12.5%), comparing Bronx demographics with national demographics.

RESULTS After dividing patients into arbitrary TSH categories ≤0.30, 0.31 to 2.49, 2.50 to 4.50 and >4.50 μIU/ml, the percentage of patients in the 0.31 to 2.49 category progressively declined with age, decreasing from 83.7% in the 20-to-29-year-old group (young) to 67.9% in the >80-year-old group (old), which was associated with a progressive increase in the percentage of patients with TSH levels in the 2.50 to 4.50 μIU/ml category

(Figure 1). Approximately 90% of the patients in the TSH >4.50 μIU/ml category had serum TSH concentrations <10 μIU/ml, which suggested a shift to higher TSH levels with aging. A comparable shift in TSH distribution with age occurred in the major racial subpopulations within the study. In whites, the percentage of patients in the 0.31 to 2.49 μIU/ml TSH category decreased from

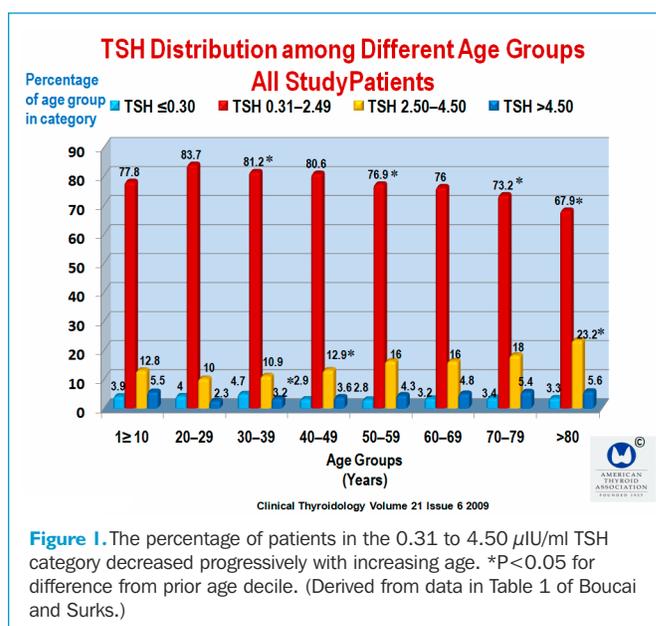


Figure 1. The percentage of patients in the 0.31 to 4.50 μIU/ml TSH category decreased progressively with increasing age. *P<0.05 for difference from prior age decile. (Derived from data in Table 1 of Boucai and Surks.)

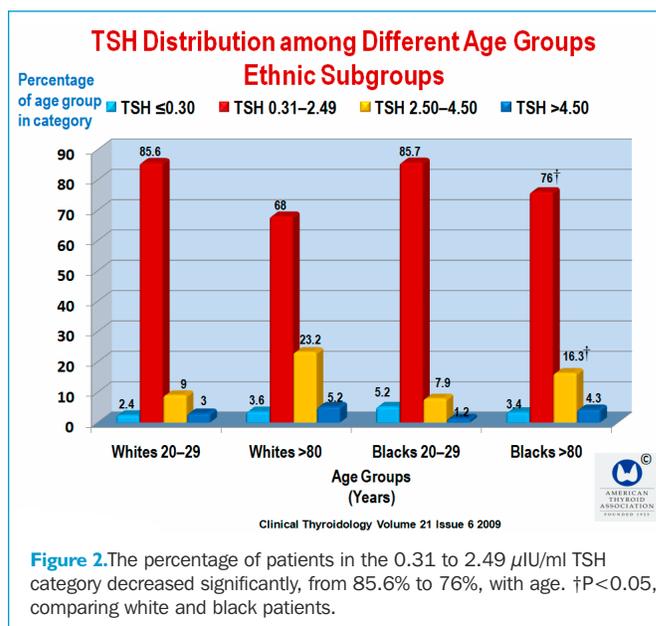


Figure 2. The percentage of patients in the 0.31 to 2.49 μIU/ml TSH category decreased significantly, from 85.6% to 76%, with age. †P<0.05, comparing white and black patients.

85.6% in the young to 68% in the old group, which was associated with an increase in patients in the 2.50 to 4.50 and >4.50 $\mu\text{IU/ml}$ categories with age (Figure 2). Furthermore, the TSH distribution of whites shifted significantly to higher TSH levels than those in blacks, including the peak TSH levels. The median and 97.5th centile for TSH in whites (1.54 and 7.46 $\mu\text{IU/ml}$), were significantly higher than those in blacks (1.18 and 5.25 $\mu\text{IU/ml}$) ($P < 0.001$). The TSH distribution in 1103 Hispanic patients was identical to that of blacks. Furthermore, the TSH distribution curves for men and women were superimposable for all patients, including blacks, whites, and Hispanics. In all patients combined (22,116), the TSH was found to shift to the right (higher levels) with age, with a median TSH of 1.13 $\mu\text{IU/ml}$ and 1.61 $\mu\text{IU/ml}$, and the 97.5th centile 5.13 $\mu\text{IU/ml}$ and 6.77 $\mu\text{IU/ml}$ for young and old, respectively ($P < 0.001$) (Figure 3). Moreover, there were similar population shifts in TSH distribution to higher concentrations with aging in each racial group (Figure 4). The median TSH level was significantly different

among young and old whites (1.24 and 1.74 $\mu\text{IU/ml}$, respectively; $P < 0.007$) and between young and old blacks (1.01 and 1.45 $\mu\text{IU/ml}$, respectively; $P < 0.001$) (Figure 5).

The mean FT_4 decreased progressively as TSH increased (P for trend < 0.001) (Figure 6). This occurred in all patients, including the subgroups young, old, blacks, and whites. The increment in FT_4 when the TSH was ≤ 0.3 $\mu\text{IU/ml}$, in comparison with the 0.31 to 2.49 $\mu\text{IU/ml}$ category, indicating that some patients may have thyroid hormone hypersecretion. The mean (\pm SD) FT_4 was not significantly different in the young and old groups (18.02 ± 4.5 vs. 17.76 ± 3.6 pmol/L; $P = 0.11$). However, mean FT_4 was higher in the white population than in the black population (18.3 ± 3.99 vs. 17.5 ± 4.38 pmol/L; $P < 0.001$). In a separate analysis, whites had significantly higher mean FT_4 levels than blacks in all TSH categories. Using the 2.5th centile for TSH from NHANES III (0.45 $\mu\text{IU/ml}$) 5.7% of all patients and 8% of blacks and 3.7% of whites

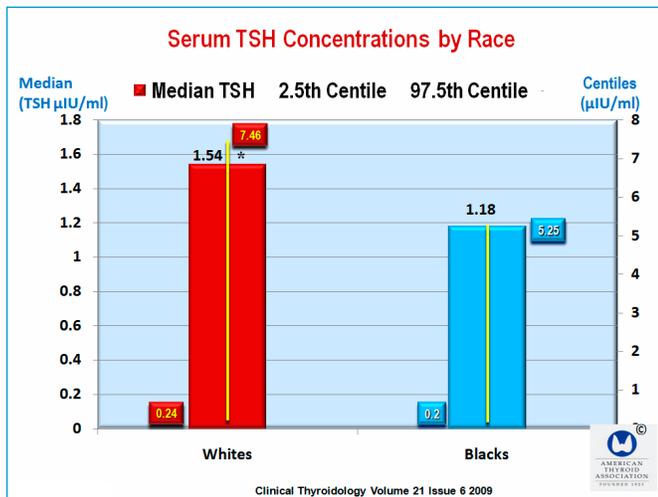


Figure 3. The median and 97.5th centile for TSH in whites were significantly higher than the median and 97.5th centile in blacks. * $P < 0.001$. The yellow lines represent the 25th and 97.5th centiles.

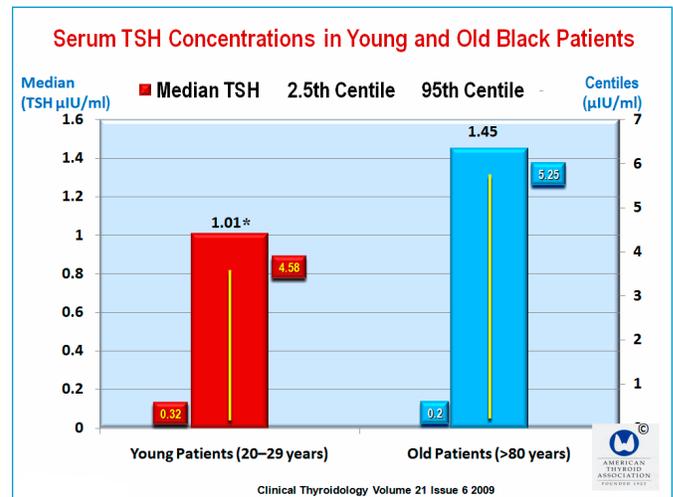


Figure 5. The median TSH and 97.5th centiles were higher in young black patients than in old black patients. * $P < 0.001$. The yellow lines represent the 25th and 97.5th centiles.

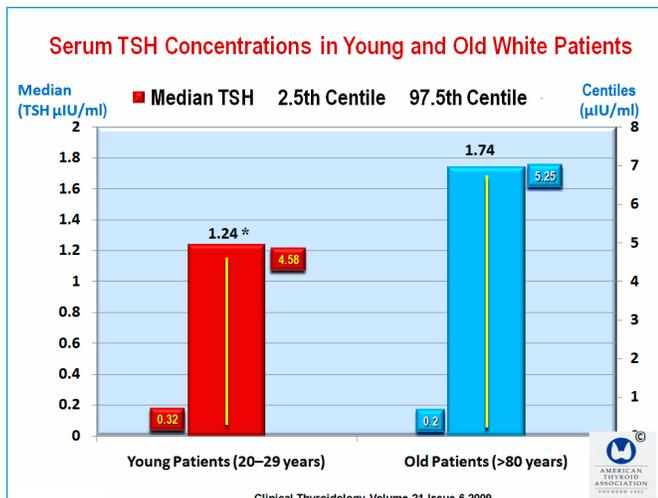


Figure 4. The median TSH and 97.5th centile were higher in older patients than in young patients * $P < 0.001$. The yellow lines represent the 25th and 97.5th centiles.

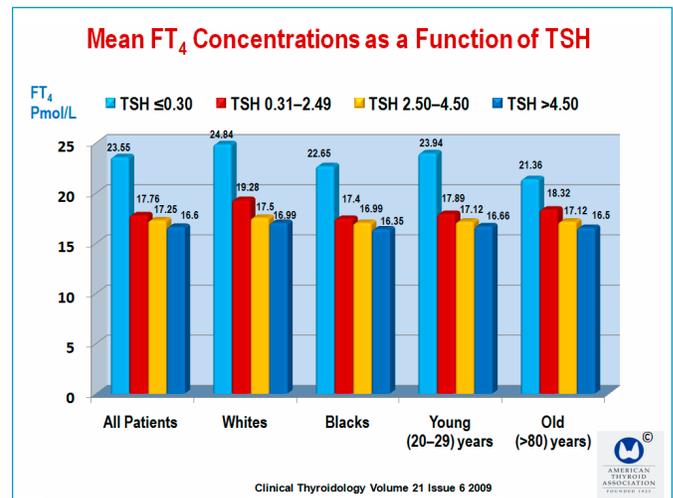


Figure 6. The mean FT_4 was significantly lower in blacks than in whites ($P < 0.001$) and did not differ between young and old, but decreased progressively (average, 7%) as TSH increased to > 4.50 $\mu\text{IU/ml}$.

would be misclassified as having elevated serum TSH levels. Using the 97.5th centile from NHANES III (4.12 $\mu\text{IU/ml}$), 4.1% of blacks and 5.8% of whites would be misclassified as having elevated serum TSH levels.

COMMENTARY

This important study has major implications for the diagnosis of thyroid dysfunction. The study shows that the reference limits for TSH differ significantly with age and between races, indicating that race- and age-specific reference limits should be routinely used in practice. The patients in this study were judged to be clinically free of thyroid disease without excluding patients with antithyroid antibodies. This was done on the basis of three studies (1-3) that found no difference in median TSH and the 97.5th centile when individuals with antithyroid antibodies were excluded. Furthermore, the NHANES III survey showed that age-related shifts in TSH distribution were not significantly changed when individuals with antithyroid antibodies were excluded. Moreover, analysis of the NHANES III survey found that age-related shifts in TSH distribution were not significantly changed when individuals with antithyroid antibodies were excluded (3).

The main findings in this study were that TSH was higher in whites as compared with blacks, and in old patients (>80 years) as compared with young patients (20 to 29 years). Using TSH limits from national databases resulted in a significant misclassification that raised or lowered TSH concentrations. In all patients, blacks, and whites, 3%, 8% and 5%, respectively, of those older than 80 years were misclassified as having high TSH as compared with those 20 to 29 years of age. The NHANES III data suggest that blacks may have lower TSH levels than whites; blacks had a significant decrease in the median, 2.5th and 97.5th centiles as compared with whites, which was confirmed by this study.

The mean FT_4 decreased progressively as TSH increased to >4.50 $\mu\text{IU/ml}$ and was lower in blacks than in whites but did not

CONCLUSION Reference limits for TSH differ between races and with age and unless age-specific limits for TSH are used, the clinical diagnosis is misclassified in a significant number of patients.

differ between young and old. As TSH increased to the >4.50 $\mu\text{IU/ml}$ category, the decrement in mean FT_4 was 6.5% for all patients, 7% for whites, 6% for blacks, and 8.4% for young and old. The authors suggest that when the TSH was ≤ 0.30 $\mu\text{IU/ml}$, in comparison with the 0.31 to 2.49 category, some patients may have hypersecretion of thyroid hormone. The implications of this are not clear and require further study. Nonetheless, regardless of the TSH level, the mean FT_4 concentration was not significantly different from that in the old group (>80 years). However, mean FT_4 was significantly higher in whites than in blacks and was significantly higher in all TSH categories.

The debate concerning the diagnosis of subclinical thyroid disease began in 2004 when Surks et al. (4) published a review and guidelines for the diagnosis and management of subclinical hypothyroidism and hyperthyroidism. Since then, the debate has swirled around the upper reference limits for TSH, which directly translates into the threshold for thyroid hormone-replacement therapy. However, in the past several years, Surks and his associates have been carefully studying the features that weave the fabric of our knowledge concerning the subtleties in serum TSH concentrations in normal individuals, which have a compelling impact on clinical decisions that will especially affect patients with subclinical thyroid dysfunction. This article and another just published article (5) that was highlighted in the May issue of *Clinical Thyroidology* set the standard for our understanding of the subtle changes in TSH with age, which will likely change our practice.

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The optimal time interval to increase radioiodine uptake in a multinodular goiter is 24 hours after recombinant human thyrotropin administration

Fast S, Nielsen VE, Grupe P, Bonnema SJ, Hegedus L. Optimizing ¹³¹I uptake after rhTSH Stimulation in patients with nontoxic multinodular goiter: evidence from a prospective, randomized, double-blind study. J Nucl Med 2009;50:732-7.

SUMMARY

BACKGROUND Recombinant human thyrotropin (TSH)- (rhTSH) has been undergoing study for the past several years for the preparation of radioiodine (¹³¹I) treatment of patients with multinodular goiter, which has not yet been approved by the Food and Drug Administration for this indication. The aim of this study was to determine the optimal time interval between rhTSH administration and ¹³¹I administration to enhance radioactive iodine uptake (RAIU).

METHODS This randomized, placebo-controlled, double-blind study was performed on patients referred for ¹³¹I treatment of symptomatic multinodular goiter at the Nuclear Department of the Odense University Hospital in Odense, Denmark. Inclusion criteria were a multinodular goiter defined as a thyroid gland with two or more nodules larger than 1 cm determined by ultrasound. Patients routinely had a clinical evaluation, thyroid-function tests and neck ultrasound examination. Goiter volume was estimated by ultrasound except for large goiters that required magnetic resonance imaging (MRI) to estimate goiter volume with or without retroclavicular extension. Fine-needle aspiration biopsy was performed on scintigraphically dominant hypoactive nodules. The exclusion criteria were age younger than 18 years, women of childbearing potential not taking contraceptives, previous ¹³¹I therapy, the use of levothyroxine or antithyroid drugs, a history of ischemic heart disease, fine-needle aspiration biopsy cytology that was inconclusive or suggestive of thyroid cancer, or multiple endocrine neoplasia, rapid goiter growth, firm nodules or fixation to adjacent structures, vocal-cord paralysis, regional lymphadenopathy, or an elevated serum calcitonin, urinary incontinence, alcohol or drug abuse, and physical or psychiatric disabilities.

The patients were randomly assigned to receive either a gluteal injection of 0.1 mg of rhTSH (n = 60) or an isotonic saline placebo (n = 30) given 24, 48, or 72 hours before the administration of a ¹³¹I tracer, after which an RAIU test was performed at 24 and 96 hours. Four weeks later, RAIU testing was repeated 24 and 96 hours after the administration of rhTSH. Before screening and enrollment, blood tests were obtained for serum thyroxine (T₄), triiodothyronine (T₃), calcitonin, and thyrotropin (TSH). The serum free T₄ index and T₃ index were calculated by multiplying the total T₄ values by the percentage of T₃ resin uptake. Thyroidal RAIU was determined 24 and 96 hours after the oral administration of 24 mCi (0.5 MBq) of ¹³¹I. Data were presented as frequencies and medians (range) or as means (±SD or ±SEM), depending on the normality of the data.

RESULTS The study subjects were 90 patients, 78 women (87%) and 12 men (13%), with a median age of 52 years (range, 22 to 83). All patients completed the study. There were no statistically significant differences in age, sex, smoking status, goiter size, number of patients who had undergone hemithyroidectomy, serum TSH, and FT₄ index or baseline RAIU.

The absolute changes in mean 24-hour RAIU: RAIU did not change significantly from baseline in the placebo group. In the study group, the mean (±SD) RAIU increased from 33.8±2.3% to 66.0±1.8% within a 24-hour interval, from 36.8±2.1% to 64.6±2.7% within a 48-hour interval, and from 33.0±2.7% to 49±2.5% within a 72-hour interval (P<0.001 for all within-group changes) (Figure 1). The effect of rhTSH was negatively correlated with the initial RAIU (r = -0.703, P<0.001).

The relative increase in 24-hour and 96-hour RAIU: In the

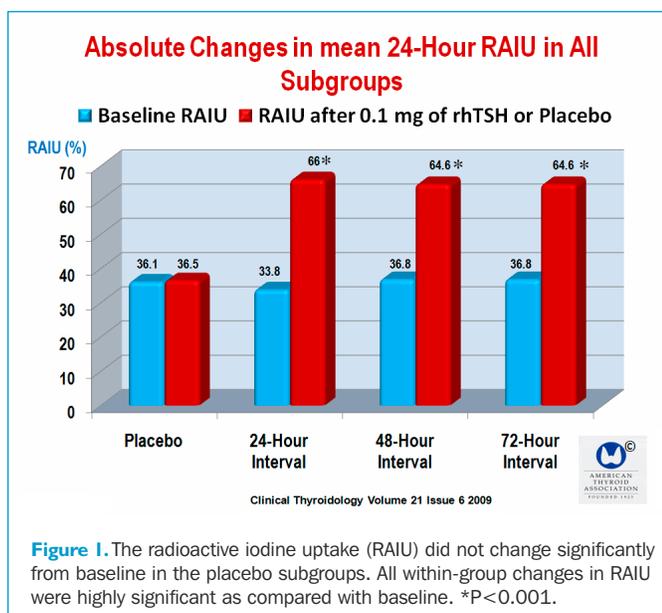


Figure 1. The radioactive iodine uptake (RAIU) did not change significantly from baseline in the placebo subgroups. All within-group changes in RAIU were highly significant as compared with baseline. *P<0.001.

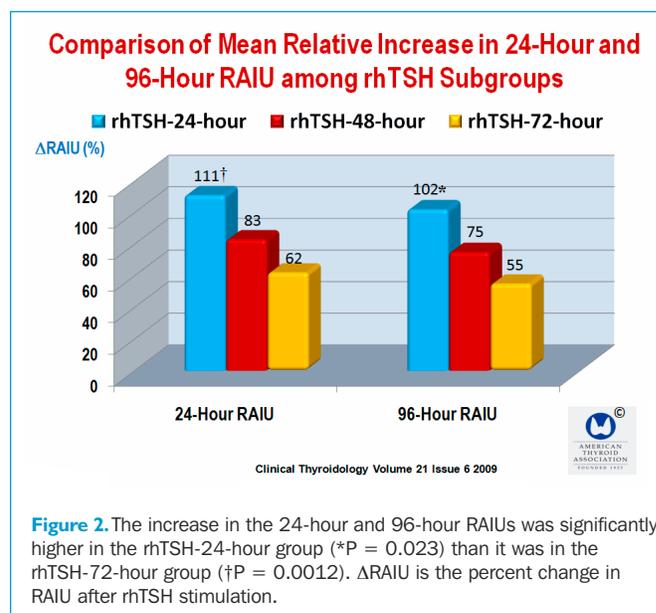


Figure 2. The increase in the 24-hour and 96-hour RAIUs was significantly higher in the rhTSH-24-hour group (*P = 0.023) than it was in the rhTSH-72-hour group (†P = 0.0012). ΔRAIU is the percent change in RAIU after rhTSH stimulation.

rhTSH-24-hour group, the mean (\pm SD) RAIU increased from $33.8\pm 9.8\%$ to $66.0\pm 7.7\%$ (mean relative increase, $111.2\pm 15.5\%$) and the rhTSH-96-hour RAIU increased from $33.5\pm 10.5\%$ to $62.5\pm 9.3\%$ (mean [\pm SEM] relative increase, $102.\pm 13.9\%$ [SEM]). In the rhTSH-48-hour group, the mean 24-hour RAIU increased from $36.8\pm 9.3\%$ to $64.6\pm 12\%$ (mean relative increase, $83.3\pm 11.0\%$) and the rhTSH 96-hour RAIU increased from $37.5\pm 9.8\%$ to $63.7\pm 13.6\%$ (SEM) (mean [\pm SEM] relative increase, $74.9\pm 8.7\%$). In the rhTSH-72-hour group, the mean 24-hour RAIU increased from 33.0 ± 11.9 to $49.6\pm 11.3\%$ (mean relative RAIU increase $62.4\pm 10.5\%$) and the 96-hour RAIU increased from $33.9\pm 11\%$ to $49\pm 11.6\%$ (mean

[\pm SEM] relative increase, $55\pm 10.3\%$; all changes in RAIU and rhTSH subgroups were significant ($P<0.001$) (Figure 2). There was a strong correlation between baseline 24-hour RAIU and the increase in 24-hour RAIU after rhTSH stimulation.

A post hoc analysis found that the mean relative increase in 24- and 96-hour RAIU in the rhTSH-24-hour group was significantly higher than the increase in the rhTSH-72-hour group ($P = 0.023$ and 0.012 , respectively).

CONCLUSION In patients with MNG the optimal time interval to increase radioiodine uptake is 24 hours after rhTSH injection.

COMMENTARY

Administering rhTSH to prepare patients with multinodular goiter (MNG) for ^{131}I therapy is a significantly different clinical scenario than administering the drug to patients with thyroid cancer who have undergone total or near-total thyroidectomy. The problem, of course, is that rhTSH stimulates the release of thyroid hormones in patients with MNG. Only 0.1 mg of rhTSH was administered in this study by Fast et al. This small amount of rhTSH is required for patients with goiter being prepared for ^{131}I therapy.

In one of the earliest studies, Huysmans et al. (1) tested 15 patients with nontoxic goiter after being given 0.01 or 0.03 mg of rhTSH before a ^{131}I tracer of 20 to 40 mCi. After 0.01 mg, FT_4 increased from 16.0 ± 2.6 to 18.5 ± 3.7 pmol/L ($P<0.0001$) and T_3 increased from 2.10 ± 0.41 to 2.63 ± 0.66 nmol/L ($P<0.0001$). After 0.03 mg, FT_4 increased from 15.2 ± 1.5 to 21.7 ± 2.9 pmol/L ($P<0.0001$), and T_3 increased from 1.90 ± 0.43 to 3.19 ± 0.61 nmol/L ($P<0.0001$). FT_4 and T_3 levels peaked 8 to 96 hours after rhTSH injection. Administering 0.01 mg 2 hours before ^{131}I increased the 24-hour RAIU from $30\pm 11\%$ to $42\pm 10\%$ ($P<0.02$), and administering the same dose of ^{131}I 24 hours before ^{131}I , the 24-hour RAIU increased from 29 ± 10 to $51\pm 10\%$ ($P<0.0001$). Administering 0.03 mg of rhTSH 24 hours before ^{131}I increased 24-h RAIU from $33\pm 11\%$ to $63\pm 9\%$ ($P<0.0001$), and after giving 0.01 mg of rhTSH 2 hours before ^{131}I , the 24-hour RAIU did not increase in 1 patient, and increased to less than 10% in 2 other patients. However, administering rhTSH 24 hours before ^{131}I increased 24-hour RAIU by more than 10% in all 14 patients, increasing to $>20\%$ in 10 and $>30\%$ in 6 patients.

In subsequent studies (1-6), differing amounts of rhTSH were administered to patients with MNGs, raising the question about

whether different doses of rhTSH might have a major effect on outcome. A study by Nieuwlaet et al. (4) that compared the use of 0.01 mg with 0.03 mg of rhTSH in patients with MNG found an 87% increase in mean RAIU using 0.01 mg, as compared with a significantly higher rate of 145% when 0.03 mg was administered. Still, other studies find no differences between the two doses (7). For example, an open label study by Braverman and Kloos (5) designed to assess the safety, adverse effects, and RAIU in response to rhTSH tested 0.03, 0.1 mg, and 0.3 mg doses in 29 patients with small nodular goiter. After evaluating the patients at 6, 24 and 48 hours, that RAIU doubled at each time point as compared with baseline uptake. Small increases in serum thyroxine and triiodothyronine occurred in some patients, along with mild symptoms of hyperthyroidism in a few patients, especially after 0.3 mg. There was a flat dose–response curve over the range of rhTSH doses tested, each of which approximately doubled thyroidal RAIU.

The study by Fast et al. clearly demonstrates that the effect of rhTSH on thyroidal RAIU is time-dependent, with a steady decline over time. However, the authors suggest that the lack of a statistically significant difference between the effects observed in the 24-hour and 48-hour subgroups are likely due to the lack of study power. The finding of a negative correlation between the increase in 24-hour RAIU and the baseline serum TSH concentration is a novel and potentially clinically important finding. The findings of this study clearly indicate that the optimal time interval that maximally increases ^{131}I therapy is 24 hours after the administration of rhTSH. However, the authors nonetheless caution that whether this time interval is optimal for goiter reduction is yet to be established.

Ernest L. Mazzaferri, MD, MACP

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Anemia in Graves' disease is common and resembles the anemia of chronic disease

Gianoukakis AG, Leigh MJ, Richards P, Christenson PD, Hakimian A, Fu P, Niihara Y, Smith TJ. Characterization of the anaemia associated with Graves' disease. Clin Endocrinol (Oxf) 2009;70:781-7.

SUMMARY

BACKGROUND Anemia sometimes develops in patients with Graves' disease; the cause of this anemia is uncertain. The aim of this study was to define the prevalence and characteristics of anemia associated with Graves' disease.

METHODS The study subjects were patients with newly diagnosed Graves' disease treated in the Endocrine Clinic at Harbor-UCLA Medical Center. A total of 98 patients were initially recruited for the study if they had anemia based on standard clinical and laboratory criteria and were already being treated with β -blockers. Patients who had been treated with thionamides or corticosteroids were excluded from the study, as were patients who had silent thyroiditis, were euthyroid, or did not have a complete blood count. The remaining 87 patients comprise the study group, which was then divided into two groups: those with anemia (group A) and those without anemia (group B). Ten women and 9 men without hyperthyroidism or any known autoimmune disease were randomly recruited from the primary care clinic to serve as controls (Figure 1).

RESULTS A total of 31 patients (36%) were in group A, and 56 (64%) were in group B. There were 12 men and 19 women in group A and 12 men and 44 women in group B (Figure 2). The mean age was 37 years (range, 19 to 53) in group A and 36 (range, 19 to 63) in group B. Of the 87 patients in the study group with Graves' disease, 64 (74%) were sequentially removed from the study group to form another cohort to establish the prevalence of anemia within the study population; 45 of this group (70.3%) were women with a mean (\pm SD) age of 37.5 ± 11.3 years, 21 of whom (33%) had anemia, with a hemoglobin (Hgb) level below the lower reference limits of 11.9 to 14.9 for women and 13.9 to 16.9 for men (Figure 1). Of the 21 patients with anemia and Graves' disease, a secondary

cause of anemia was established in 7 (33%). As a result, the prevalence of anemia with no cause other than Graves' disease was 14 of 64 patients (21.9%; 95% confidence interval [CI], 12.5 to 34%) (Figure 1). Graves' disease with anemia affected 10 of 24 men (41.6%), as compared with 11 of 63 women (17.5%) (Figure 1).

Of the 21 patients with Graves' anemia, mean erythropoietin (EPO) levels were 15.5 ± 5.3 mIU/ml, which was within normal reference limits (4.1 to 19.5 mIU/ml) as compared with 11.4 ± 5 mIU/ml in the non-Graves' anemia patients ($P = 0.004$) (Figure 3). With

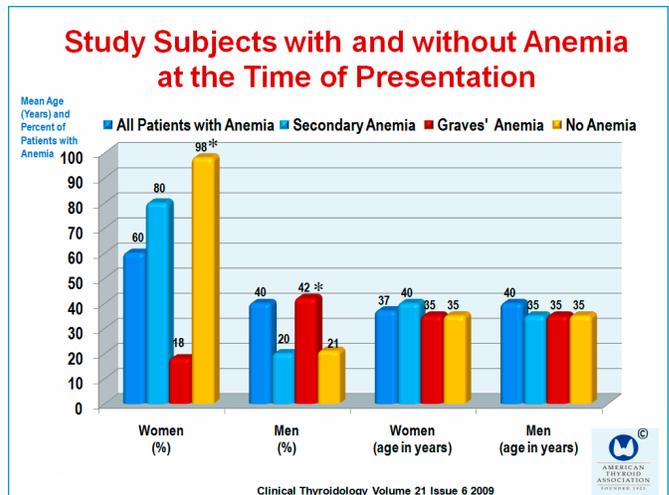


Figure 2. Women were more likely than men (98% vs. 21%) to have anemia. Most of the women in the study were in mid-life.

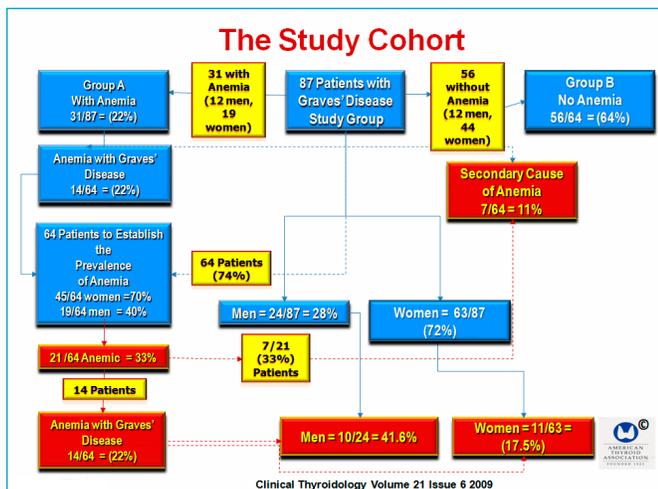


Figure 1. The study cohort comprised patients with Graves' disease and anemia and patients with Graves' disease and secondary causes of anemia. A greater percentage of men (41.6%) than women (17.5%) had anemia with Graves' disease. This figure shows the flow of the study.

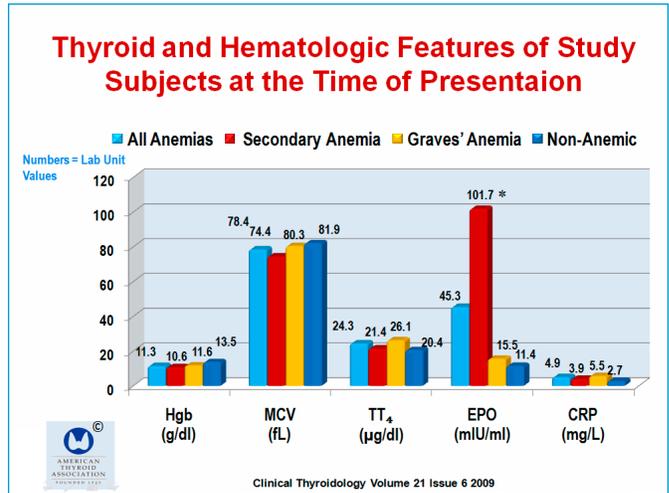


Figure 3. Hemoglobin (Hgb), mean corpuscular volume (MCV), total thyroxine (TT₄), C-reactive protein (CRP), and erythropoietin (EPO) levels are shown in patients with Graves' anemia, in those with secondary anemias, and in patients without anemia * $P < 0.005$ comparing EPO levels with secondary anemia and Graves' disease with anemia. fL = femtoliter

Change in Hematologic Parameters during Restoration of Euthyroidism (1)

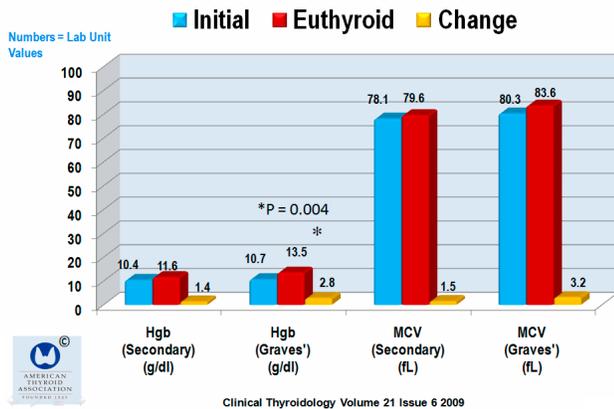


Figure 4. This figure shows the change in hematologic parameters during restoration of euthyroidism. Hgb = hemoglobin; MCV = mean corpuscular volume.

antithyroid therapy for 16 ± 6.3 weeks, Hgb levels became normal in 8 of 9 patients (89%) with Graves' disease and anemia (10.7 ± 0.8 to 13.5 ± 1.3 g/dl, $P = 0.0001$) (Figure 4). After the Hgb returned to normal, mean corpuscular volume (MCV) and total iron-binding capacity (TIBC) increased significantly, and median ferritin and mean erythropoietin (EPO) decreased significantly (Figure 4). C-reactive protein (CRP) and ferritin, which are markers of inflammation, were not significantly higher in group A than in group B ($P = 0.09$). Total T_4 (TT_4) and total T_3 (TT_3) were not significantly correlated with Hgb levels; however, Hgb correlated inversely with CRP, and remained so after multivariate analysis, but not with ferritin levels. TIBC correlated positively with Hgb ($P = 0.0005$), while EPO levels correlated inversely with Hgb ($P = 0.05$). After patients with Graves' anemia had a significant increase in their Hgb, mean MCV, and TIBC levels, median ferritin, and mean EPO levels decreased significantly ($P = 0.0004$, 0.02 , 0.03 , and 0.04 , respectively) (Figure 5).

COMMENTARY

This study by Gianoukakis et al. of anemia in 87 patients with newly diagnosed Graves' disease found that 33% had anemia. However, about one third had secondary causes of anemia that were not due to Graves' disease. Most patients suffering from chronic infections, inflammatory diseases, and some malignancies have a mild to moderate anemia termed anemia of chronic disease or anemia of inflammation. Patients with this type of anemia generally have low serum iron, low to normal transferrin, and high to normal serum ferritin concentrations. The anemia is caused by increased inflammatory cytokines, especially interleukin-6 (1).

In a study by Das et al. (2) the bone marrow showed erythroid hyperplasia in all patients with hyperthyroidism. The authors postulated that thyroid hormones stimulate erythropoiesis, sometimes leading to erythrocytosis, provided there is no deficiency of hematopoietic nutrients.

Change in Hematologic Parameters during Restoration of Euthyroidism (2)

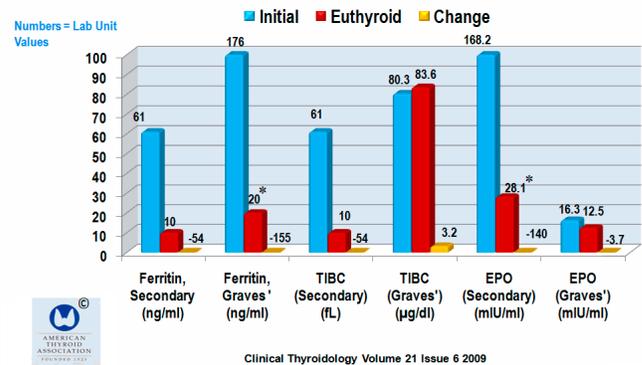


Figure 5. The levels of ferritin and total iron-binding capacity (TIBC) and erythropoietin (EPO) were significantly elevated after patients with anemia and Graves' disease were treated with antithyroid drugs or radioiodine.

With antithyroid therapy for 16 ± 6.3 weeks, Hgb levels became normal in 8 of 9 patients with Graves' anemia, increasing from 10.7 ± 0.8 to 13.5 ± 1.3 g/dl ($P = 0.0001$) (Figure 4). In patients with Graves' disease without anemia, there was a small but statistically significant increase in Hgb (0.36 ± 0.9 g/dl, $P = 0.02$) and MCV. The TT_4 and TT_3 levels correlated with an increasing Hgb in patients with Graves' disease anemia and patients with anemia of other causes. In addition, a similar inverse correlation existed between changes in Hgb and EPO levels ($P = 0.04$) (Figure 5). There was no correlation between changes in Hgb and CRP levels. Patients treated with 2.5 to 40 mg of methimazole or 50 to 600 mg of propylthiouracil did not experience worsening hematologic parameters.

CONCLUSION Anemia in Graves' disease is common and resembles the anemia of chronic disease.

In a study of 239 patients with uncomplicated hyperthyroidism, Nightingale et al. (3) found that the hemoglobin concentration was less than 12.0 g/dl in 37 (18%) of 207 women and less than 13.0 g/dl in 9 of 32 (28%) of men. Although some of the patients had iron deficiency, many did not. After treatment, the hemoglobin increased by an average of 0.5 g/dl in patients who had not had anemia at the time of diagnosis. The authors concluded that a small decline in hemoglobin is usual in hyperthyroidism and may sometimes be sufficient to cause a mild anemia. There was a reduction in MCV in patients with hyperthyroidism who had neither anemia nor reduced transferrin saturation. After treatment of hyperthyroidism, the MCV increased an average of 6 fl. Thus, a reduction in MCV, even within the normal range, is a common finding in hyperthyroidism.

Gianoukakis et al. found that with antithyroid therapy, the Hgb levels returned to normal in 8 of 9 patients, with Graves' disease anemia, and mean MCV and TIBC increased significantly, while median

ferritin and mean EPO decreased significantly. Hgb correlated inversely with CRP and remained so after multivariate analysis with adjustment for TT_3 or TT_4 . Although men comprised only 28% of the cohort, Graves' disease anemia affected 41.6% of men as compared with 17.5% of women. While this seems somewhat counterintuitive, others have also found this to be the case (3).

Still, despite the erythropoietic effects of thyroid hormone, most patients with thyrotoxicosis have normal levels of Hgb. Gianoukakis et al. postulate that the approximately 6% increase in blood volume that occurs in hyperthyroidism may

serve to partially counterbalance the erythropoiesis induced by thyrotoxicosis. Why anemia develops in a subgroup of patients is not known. Although some patients with Graves' disease have vitamin B12 deficiency, the authors of this study did not find a secondary cause for the anemia. Nonetheless, Gianoukakis et al. detected a slight but significant ($P < 0.01$) increase in the levels of Hgb after improvement of hyperthyroidism in the group without anemia. Others have made similar observations, suggesting that thyrotoxicosis routinely decreases Hgb levels (3,4).

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Preparation for ¹³¹I remnant ablation with 54 mCi is equally effective with thyroid hormone withdrawal and recombinant human TSH

Chianelli M, Todino V, Graziano FM, Panunzi C, Pace D, Guglielmi R, Signore A, Papini E. Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. *Eur J Endocrinol* 2009;160:431-6.

SUMMARY

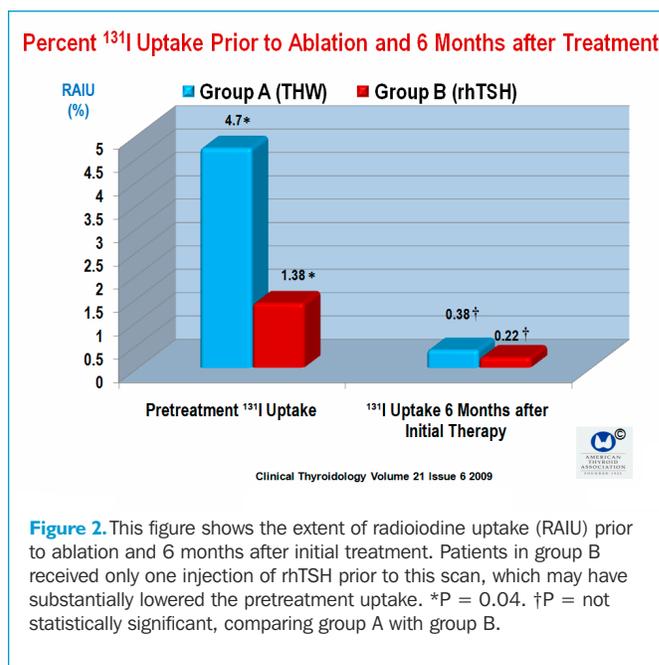
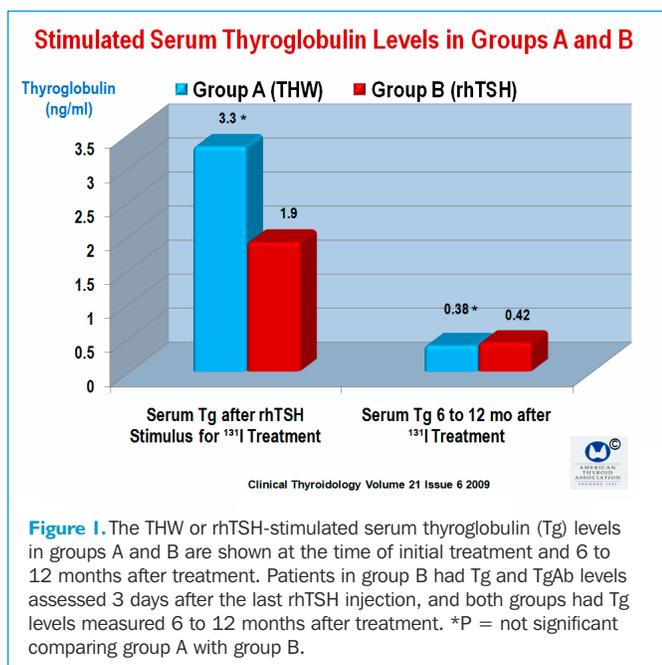
BACKGROUND Thyroid remnant ablation after total thyroidectomy has traditionally been performed after thyroid hormone withdrawal (THW). However, the subsequent hypothyroidism frequently causes fatigue, depression, difficulties with concentration, and myriad other debilitating symptoms. Thus, the development of recombinant human TSH (rhTSH) was well received by patients with thyroid cancer and their clinicians, as it offered the opportunity to perform diagnostic whole-body ¹³¹I scans without the associated morbidity of hypothyroidism. A randomized, prospective trial using 100 mCi of ¹³¹I found comparable ablation rates with THW and rhTSH. The Food and Drug Administration consequently approved the use of rhTSH to stimulate thyrotropin (TSH) levels prior to remnant ablation with 100 mCi. Whether smaller amounts of ¹³¹I will be associated with equivalent ablation rates with THW and rhTSH continues to spark research. The present study examines whether remnant ablation with 54 mCi (2 GBq) is comparable with THW and rhTSH.

METHODS All patients had papillary thyroid carcinoma (PTC) or minimally invasive follicular thyroid carcinoma (FTC), all of which were American Joint Committee on Cancer (AJCC; 5th edition) tumor–node–metastasis (TNM) stage <T1N0, a tumor 1 cm or smaller without lymph-node metastases. Cervical ultrasonography was performed in all patients to determine the absence of lymph-node metastases; all had either total thyroidectomy or near-total thyroidectomy, after which patients began levothyroxine (L-T₄) suppressive therapy. Patients with thyroglobulin antibodies were excluded from the study. All were treated with ¹³¹I for 42 to 180

days after the initial surgery. Patients were randomly assigned to one of two pretreatment groups, both of which were placed on a low-iodine diet for 2 weeks prior to ¹³¹I remnant ablation. A diagnostic ¹³¹I whole-body scan using 0.5 mCi (18 MBq) was performed 24 hours prior to administration of the ablative dose. Radioiodine uptake was also measured to determine the extent of residual thyroid tissue and to assist in pretreatment staging. Four to 6 days after the ablative dose, a posttreatment whole-body scan was obtained.

Group A was prepared for ¹³¹I remnant ablation by THW. This group comprised 21 patients (16 women [76%], 5 men [24%]) whose mean (±SD) age was 48±9.9 years. L-T₄ was stopped for 37 days; from the 3rd to the 22nd day after L-T₄ withdrawal, patients were treated with triiodothyronine (T₃). This group was treated with 54.6±5.9 mCi (2.02±.22 GBq)

Group B was prepared for ¹³¹I ablation with two daily injections of rhTSH. This group comprised 21 patients (17 women [81%], 4 men [19%]) whose mean age was 46.2±12.3 years. In 18 patients (86%) the tumors were papillary or follicular variant PTC, and the others were follicular tumors. This group was prepared for ¹³¹I therapy with two daily 0.9-mg injections of rhTSH and was treated with 53.2±4.9 mCi (1.97±0.18 MBq) of ¹³¹I 24 hours after the last injection of rhTSH. For both groups, the success rate of remnant ablation was determined by a diagnostic whole-body scan performed 6 to 12 months after the treatment. Stimulation for this scan was performed with THW, and images were acquired 48 hours after the 5-mCi (185-MBq) dose of ¹³¹I. Serum samples



were obtained for TSH, free T₄ (FT₄), thyroglobulin (Tg), anti-Tg antibodies (TgAb), and urinary iodine excretion.

RESULTS There was no statistically significant difference in serum TSH levels at the time of treatment in groups A and B (77.9±17.1 vs. 91.00±9.8). Although the stimulated serum Tg levels at the time of treatment were slightly lower in the rhTSH group (1.9±2.15 ng/ml) than in the THW group (3.3±3.7 ng/ml), this difference was not statistically significant (Figure 1). The pretreatment ¹³¹I uptake scan was significantly different between

the two groups: the THW patients had a higher cervical ¹³¹I uptake (4.7±4.55%) than the rhTSH group (1.38±1.14%) (P = 0.004) (Figure 2). However, patients in the rhTSH group had received only one injection at the time of the pretreatment scan, and therefore were not likely to have fully elevated TSH levels.

Evaluation for thyroid remnants was performed by ultrasonography; 5 patients in the THW group had a discernible remnant ¹³¹I uptake as compared with 4 patients in the rhTSH group. In all cases the remnant volume was less than 1 ml. There was neither a significant difference in volumes of remnant tissue between the two groups nor an association between remnant sizes as measured by ultrasonography or ¹³¹I uptake or ablation rate.

High rates of successful ablation were observed in both groups at the 6-month follow-up. There was no ¹³¹I uptake in the diagnostic whole-body scan in 20 of 21 patients (95.2%) in group A and in 19 of 21 patients (90.5%) in the rhTSH group (group B) (P = not significant) (Figure 3). When analyzing the stimulated Tg as a measure of successful ablation, there were 20 evaluable patients, one of whom had undetectable levels at the time of treatment. Thus, Tg could not be used as an objective indication of complete ablation. Still, if a serum Tg <1 ng/ml were used to assess the efficacy of therapy, the rate of successful ablation was 90% in group A and 85% in group B (P = not significant). The three patients with mildly elevated stimulated Tg levels had values of 1.08, 1.12, and 1.37 ng/ml 6 to 12 months after treatment. In all patients in both groups, the Tg levels were undetectable while on L-T₄ suppressive therapy.

CONCLUSION In low-risk patients, preparation for ¹³¹I ablation with 54 mCi has similar efficacy with THW or rhTSH stimulation based on comparable rates of negative diagnostic whole-body scans and stimulated Tg <1 ng/ml 6 to 12 months after therapy.

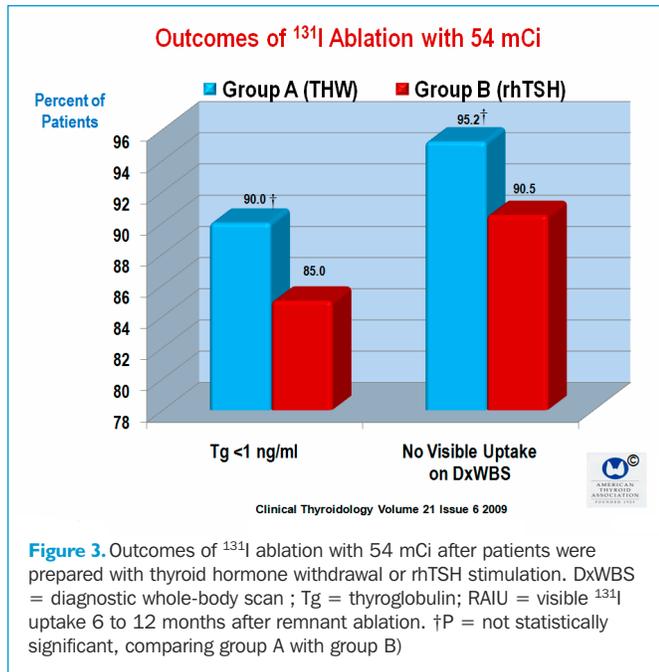


Figure 3. Outcomes of ¹³¹I ablation with 54 mCi after patients were prepared with thyroid hormone withdrawal or rhTSH stimulation. DxWBS = diagnostic whole-body scan ; Tg = thyroglobulin; RAIU = visible ¹³¹I uptake 6 to 12 months after remnant ablation. †P = not statistically significant, comparing group A with group B)

COMMENTARY

Whether to perform remnant ablation in patients with low-risk thyroid cancer is a controversial issue among endocrinologists (1,2). There are retrospective cohort studies that have found that its use significantly reduces the risk of recurrence and may improve mortality (3,4), whereas other studies (5,6) have shown no such benefit, especially when total thyroidectomy and prophylactic lymph-node total compartment dissection is performed (7). Postoperative surveillance is more sensitive, however, when remnant ablation is used. Patients who have not received radioiodine will continue to have measurable levels of Tg, making it impossible to differentiate benign from malignant sources. This is especially problematic, since both the American and European thyroid associations recommend that, in addition to negative clinical examination and imaging studies, serum Tg should be undetectable (<1 ng/ml) during TSH suppression and stimulation in the absence of interfering anti-Tg antibodies to reach a firm conclusion that a patient is free of disease (8,9). Thus, endocrinologists and patients often prefer to use radioiodine to simplify postoperative surveillance. Because thyroid hormone withdrawal is associated with significant morbidity, the possibility of substituting recombinant human TSH in preparation for remnant ablation has great attraction, particularly in low-risk patients. A recent multicenter trial showing comparable

ablation rates with THW and rhTSH when using 100 mCi (10) has stimulated a number of other studies to investigate the use of rhTSH with small amounts of radioiodine in the range of 30 to 50 mCi.

Many clinicians would prefer to administer smaller amounts of ¹³¹I to low-risk patients to minimize the associated risks of salivary-gland dysfunction and secondary malignancies. A study (11) that evaluated the efficacy of rhTSH and THW with 30 mCi for ablation showed that this dose is insufficient for a satisfactory ablation rate with rhTSH stimulation. In a subsequent study (12), the authors postulated that the reduced rates of successful ablation in the rhTSH group were the result of interference of excess iodine in the L-T₄ tablets. To test this theory in patients who received rhTSH, the authors of the study stopped L-T₄ the day prior to the first injection of rhTSH and restarted it the day after ¹³¹I ablation. Ablation rates based on 12-month rhTSH-stimulated diagnostic whole-body scans and Tg levels were not significantly different between the patients initially stimulated with THW and those stimulated with rhTSH. These findings are encouraging concerning the possibility of using smaller amounts of ¹³¹I with rhTSH stimulation, but further study of 30 mCi with rhTSH is needed to clarify these conflicting results. In the meantime, clinicians seeking to perform low-dose

remnant ablation may effectively use 50 mCi (13) to 54 mCi (the study under discussion) when stimulating with rhTSH.

More prospective studies are also needed to evaluate the efficacy of rhTSH-stimulated ablation of metastatic disease. However, there are several retrospective studies (14-16) that report successful remnant ablation in patients with lymph-node and distant metastases treated on a compassionate-use basis. rhTSH is not approved by the Food and Drug Administration for routine clinical treatment of distant metastases. Caution must be exercised when opting to treat patients with distant metastases—particularly those with tumor in enclosed spaces—because cases have been reported of sudden enlargement of neoplastic tissue after the stimulation with rhTSH, especially in elderly patients (17).

Long-term prospective data on the outcomes of patients treated with rhTSH-stimulated remnant ablation are likewise lacking. It is currently unknown whether the equivalence of remnant ablation using rhTSH and THW in preparation for ¹³¹I therapy translates into comparable recurrence and mortality rates in the long term. A recent retrospective study (18) of patients treated with rhTSH-stimulated ablation compared to a historical control group that had THW found that the rates of persistent disease were lower in the rhTSH group, and that more patients had no clinical evidence of disease in the rhTSH group (P = 0.02). If these findings are reproducible in a prospective trial, the implications of administering rhTSH stimulation prior to remnant ablation may go beyond making patients feel better by not becoming hypothyroid.

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HOT NEW ARTICLES

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DISCLOSURE

Dr. Mazzaferri receives honorari from Genzyme for providing lectures,

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.

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